REMARKS

STATUS OF THE CLAIMS

Claims 1-2 and 8-24 are pending, and claims 8-23 remain withdrawn as directed to nonelected subject matter. Claims 1, 2 and 24 are presently under active prosecution.

Claims 3-7 are previously canceled, without prejudice.

No new matter is added.

AMENDMENTS TO THE CLAIMS

Claim 1 is amended to more particularly set forth Applicants' invention at step (c) of the claimed process. Support for the wording of the phrases of amended claim 1(c) that are identified by superscript numbers 1-3 and italics is summarized below.

> c) conducting a structural comparison between the VH and VL variable regions of the animal antibody and the VH and VL regions of the framework acceptors of human origin, respectively and [1]*comparing the value of the root mean square deviation (RMS) calculated between atoms of alpha carbon constituting the respective amino acid skeletons not considering atom pairs with an RMS exceeding 2Å*, [2]*comparing percentages of atoms on which RMS was calculated,* [3]*and comparing a similitude index between primary structures to identify the VH region and the VL region of human origin with the smaller RMS*; and ...

The above-numbered clauses of amended claim 1(c) are respectfully submitted to be supported by the specification as follows.

Clause [1] is supported, for example, at page 13, lines 16-19 of the instant patent application.

Clause [2] is supported, for example, at page 13, lines 19-22 of the instant patent application.

Clause [3] is supported, for example, at page 13, lines 23-24 and page 13, lines 31-32, and particularly the text bridging pages 12-14.

The amendments are also submitted to be supported by the application figures, because the figures illustrate that three variables are employed in the claimed method, based on the three axis of e.g., Figs. 3 and 4, as discussed, for example, in the paragraph bridging pages 34-35.

No new matter is added.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

At pages 3-5 of the Office Action dated April 1, 2011, claims 1, 2 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Pedersen et al. ("Pedersen;" US 5,639,641) in view of Ramsland et al. The cited art is fully addressed hereinbelow.

At page 6 of the Office Action, the Examiner has expanded on her previous reasoning in this rejection, quoting Pedersen, at Col. 28, lines 30-67. In particular, the Examiner has underlined and italicized the statement by Pedersen that the "two domains are then paired by least squares fitting on the most conserved strands of the antibody beta barrel..." The Examiner argues that "it is very well known in the art that said RMSD is calculated using a least-squares fitting." The Examiner concedes that the "mouse model was not produced crystallographically" but cites Ramsland as remedying this deficiency.

Applicants respectfully disagree. As explained in the previous Response, dated June 6, 2011, the contents of which are incorporated by reference herein, the law requires that the claims must be considered as a whole, e.g., Manual of Patent Examining Procedure (MPEP) §2141.06(I). The MPEP explains that:

> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). [Emphasis in original].

The Examiner's attention is respectfully directed to claim 1(c) that makes it clear that the inventive process requires a comparison between the human and nonhuman variable domains based on three variables. These are:

> [1] comparing the value of the root mean square deviation (RMS) calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å,
> [2] comparing percentages of atoms on which RMS was calculated, and
> [3] comparing a similitude index between primary structures to identify the VL region of human origin with the smaller RMS; and ...

With claim 1 in mind, the Examiner's attention is respectfully directed to the disclosures of Pedersen, e.g., the Pedersen method steps at, e.g., Pedersen Cols. 5-6 and/or Pedersen claim 1, "a

method for producing a humanized rodent antibody or fragment thereof by resurfacing, said method consisting essentially of..." reciting steps (a) through (i).

Based on the above, the Pedersen method requires:

> -that the heavy and light chain variable region framework surface exposed positions be selected because they are at least 98 % identical between rodent and human [step (a)];
>
> -that the heavy and light chain variable region framework surface exposed amino acid residues of the rodent antibody be substituted with the human ones [steps (b) through (d)];
>
> -further identifying amino acid residues that are within 5 Ångstroms of any atom of any residue of the complementarity determining regions of the rodent antibody [steps (e) through (f)];
>
> -that the further identified amino acid residues (that are within 5 Ångstroms...) be substituted back to the original rodent amino acid residue [steps (g) through (h)].

In addition, the Examiner's attention is respectfully directed to Pedersen at column 8, second paragraph, starting with, "[t]here are several key features of the resurfacing approach of the present invention..." and enumerating features (1) through (4). In particular, feature (2) of Pedersen requires assessing solvent accessibility. The instantly claimed invention does not require this step, and this step is submitted to be at odds with, and not a compatible fit with, steps (a) through (d) of instant claim 1. In particular, the three variables of claim 1(c) are nowhere taught or suggsted by Pedersen, taken in any combination with the art of record.

As previously explained, Ramsland only mentions one instance where crystallographic investigation was applied to two pre-existing antibodies, *i.e.* humanized AF2 and mouse-human chimeric AF2. That study was designed to understand why the humanized antibody had a two-fold lower affinity for its target when compared to the chimeric antibody (p. 255, right column, second paragraph). Hence, Ramsland does not *a priori* use crystal structures for the selection of frameworks for the humanization process, but describes *a posteriori* determination of the crystal structures of pre-existing humanized and chimeric antibodies in order to understand their characteristics. Thus, Ramsland employs *a posteriori* structural information to rationalize the reasons why an already performed humanization led to loss of affinity/specificity of the humanized version. Thus, at best, Ramsland teaches about the failures of others in the field.

The Examiner concedes that Pedersen does not teach a method wherein the rodent antibody molecular model has been determined by crystallographic methods. However, it is respectfully submitted that the difference goes beyond employing crystallographic methods. The instantly claimed invention is submitted to be a completely different process than the process that is described by Pedersen and Ramsland, taken in any combination. The mere mention of crystallographic methods by Ramsland would have failed to teach or suggest the instantly claimed invention to the ordinary artisan, because nowhere are the specifically claimed process steps described or even hinted at.

The methods of claim 1, *et seq.*, require, in outline form:

> a) obtaining a crystallographic structure of the VH and VL regions of the animal antibody; ...
> b) pre-selecting a series of 0 to n possible framework acceptors of human origin or humanized antibodies, ...
> c) conducting a structural comparison between the VH and VL variable regions of the animal antibody and the VH and VL regions of the framework receptors of human origin...and comparing the value of the root mean square deviation (RMS) calculated between atoms of alpha carbon constituting the respective amino acid skeletons, not considering atom pairs with an RMS exceeding 2Å, comparing percentages of atoms on which RMS was calculated, and comparing a similitude index between primary structures to identify the VL region of human origin with the smaller RMS; and
> d) inserting in appropriate position a CDR region of the animal antibody into the VH region and the VL region of human origin identified in c).

Thus, claim 1 requires seven specific steps [step (c) comprises four steps - "conducting" and three "comparing" steps] and any rejection of claim 1 must meet the legal burden to show how the cited reference(s) would have taught or suggested all of these particular process steps.

The Examiner's rebuttal, at page 6 of the Office Action, compares building the framework model of Pedersen to steps (b) and (c) of instant claim 1. However, nowhere in that comparison is it shown where Pedersen discloses step (b) of claim 1 ("pre-selecting a series of 0 to n possible framework acceptors..."). Further, nowhere in that comparison is it shown where Pedersen discloses the **four** processes of step (c) of claim 1 as listed above.

Thus, even if the skilled person would combine the teaching of Pedersen with Ramsland's s/he would not arrive at the claimed invention because so many features of the method of Pedersen would have to be replaced with features that are simply not disclosed in Ramsland.

Thus, it is respectfully urged that the Patent Office has failed to support a *prima facie* rejection based on the cited references, taken separately or in any combination.

Turning now to the Advisory Action dated June 16, 2011, where the Examiner has argued, *inter alia*, as follows.

At page 2, paragraph 7 of the Advisory Action, it is stated that:

> Thus, one skilled in the art would substitute the method of CDR grafting for CDR resurfacing, although maintain using frameworks as in Pedersen et al., just frameworks based upon crystallographic structures for the reasons recited previously and below.

It is Applicants' position that CDR grafting and CDR resurfacing are not the same. The claims and specification do not mention resurfacing.

In addition, at page 2, paragraph 9 of the Advisory Action, it is stated that:

> However, the Examiner takes the different position that Ramsland et al. teach why it is necessary to compare the 3-D structures and sequences of antibodies to by humanized and CDR grafted; e.g. that it is absolutely necessary to do so when one would select frameworks because they demonstrate that even in a loop region on the VH region having 100% identity from mouse to human, this was not enough to give rise to absolute conservation of the 3-D structure, rather, upon inspection and overlay of the structures (which is produced by a LSQ method and ultimately gives rise to rmsd calculations), it was suggested retromutation was necessary of a proline residue for a serine residue which ensured structural integrity. Thus, this would make obvious, that the very well-known method of CDR grafting would be better served by crystallographic structure comparisons (in addition to sequence identity) and that simple homology models are not sufficient to reveal subtle differences even in sequences which are identical - albeit grafted onto different frameworks.

It is not clear how the Examiner leaps from the shortcomings of the LSQ method attributed to Ramsland to making "it obvious that...CDR grafting would be better served by crystallographic structure comparisons (in addition to sequence identity)." It is respectfully submitted that this is a conclusion without basis in any facts presently of record. If the Examiner is basing her conclusions, as to Ramland or any of the other points of the rejection, on personal knowledge, she is respectfully invited to make such personal knowledge of record in a Declaration Under 37 CFR 1.132.

The Examiner is respectfully invited to reconsider her conclusions in view of the claims as now pending.

For all of these reasons, it is respectfully requested that this ground of rejection be reconsidered and withdrawn.

DOUBLE PATENTING REJECTIONS

At pages 7-8 of the Office Action, the Examiner maintained the previous *provisional* rejection of claims 1, 2 and 24 as an alleged obviousness-type double patenting over claims 1, 2 and 24 of copending Appl. Ser. No. 12/838,062. Since there is not yet any indication of allowable subject matter in the instantly claimed invention, it is considered that this is a *provisional* rejection. Applicants acknowledge the *provisional* rejection, and respectfully ask to defer a response to this rejection until there is an indication of patentable subject matter in the instant patent application.

For all of these reasons, it is respectfully requested that this ground of rejection be reconsidered in any further Office Action in view of the claim amendments provided herein.

CONCLUSION

It is respectfully submitted that application is in condition for allowance, and reconsideration and allowance is hereby requested. If any questions remain, the Examiner is respectfully requested to contact the undersigned for a telephone interview, in the interest of expeditious prosecution.

FEES

A Request for Continued Examination and the required fee is enclosed. No additonal fees are believed to be owed for entry of this Response. Nevertheless, if it is determined that any fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to Deposit Account No. 02-2275.

A Petition for Extension of Time for Two-Months is enclosed herewith, together with the fee required for a Small Entity. Nevertheless, if further extension is required, pursuant to 37 C.F.R. §1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

Should any additional fees or extensions of time be necessary in order to maintain this

Application in pending condition, appropriate requests are hereby made and authorization is given to Deposit Account No. 02-2275.

Respectfully submitted,

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